the paper and computer readable copies of the Sequence Listing submitted herewith are the same.

The specification has been amended to provide appropriate SEQ ID NOS for the sequences disclosed in the substitute Sequence Listing submitted herewith. This submission contains no new matter.

A "marked-up" version of the amendments to the specification and claims is attached to this Amendment as required by 37 C.F.R. 1.121.

OBJECTION TO THE SPECIFICATION AND CLAIMS

The Examiner objected to the specification and the claims because 1) of the use of brackets in claim 33 and in the text (citing to page 5, line 24 of the specification as an example) and 2) the citation of an amino acid sequence in claim 33 without a sequence identifier.

In response, Applicants submit that the objection to the lack of sequence identifier in claim 33 is rendered moot by the cancellation of claim 33 and the presentation of new claim 47.

With respect to the objection to the use of brackets in claim 33 and in the specification, Applicants note as an initial matter that claim 33 was, as suggested by the Examiner at page 4, lines 7-8 of the Office Action, added as a new claim in the Amendment filed September 6, 2001 and that the objected to disclosure at page 5, line 24 was in the application as originally filed and was not added by amendment. Thus, 37 C.F.R. 1.121, entitled "Manner of Making Amendments in Applications" did not apply to claim 33 or to the objected to disclosure at page 5, line 24 of the specification.

In addition, Applicants note that the use of brackets in chemical nomenclature is common and widely accepted in the chemical arts and by the Patent Office itself (as examples of the numerous patents which utilize brackets in both the specification and claims see two recently issued patents, US 6,432,996 and 6,482,844) and that the imposition of a requirement to remove brackets from the naming of chemical compounds would thus be both impractical and contrary to the accepted practices of skilled artisans in the chemical field and of the Patent Office itself.

Accordingly, Applicants submit that the use of brackets in previously filed claim 33 (and in new claim 47) and in the specification is proper and withdrawal of this objection is respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH

The Examiner rejected claims 20-26 and 34-40 under 112, first paragraph because the specification has allegedly "not shown how the fatty acid having an amino group as the lipophilic substituent is attached to the N-terminal amino acid of the peptide through Glu or Asp as the spacer, which is cited in claims 20 and 34" (page 5 of Office Action).

In response, Applicants respectfully submit that this rejection is rendered moot by the amendment to claims 20 and 34 to recite that the "lipophilic substituent is a straight chain fatty acid optionally having an amino group...". Thus, as taught by page 3, lines 4-20 of the specification, where succinic acid is the spacer, the lipophilic substituent is a straight chain fatty acid having an amino group and where Glu or Asp is the spacer, the lipophilic substituent is a straight chain fatty acid without an amino group (see page 3, lines 14-20, where the acyl group of the fatty acid is attached to the amino group of the Asp or Glu spacer and one of the carboxyl groups of Asp or Glu is attached to the amino group in the N-terminal amino acid of the peptide).

Accordingly, withdrawal of this rejection is respectfully requested in view of the aforementioned amendment to claims 20 and 34.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, SECOND PARAGRAPH

The Examiner rejected claims 20-46 as indefinite because 1) in the terms "a derivative of GLP-1 or analog or fragment thereof" or "a derivative of GLP-2 or analog or fragment thereof", it is unclear how different the derivative is as compared to the parent compound; 2) there is no antecedent basis for the specific structures recited for the lipophilic groups and spacer in claims 25, 26, 39 and 40 since the structures shown do not contain an amino group in the lipophilic substituent; and 3) in the term "Glu-Lys wherein the Lys is attached to the C-terminal amino acid or Asp-Lys wherein the Lys is attached to the C-terminal amino acid" in claims 27 and 41, it is unclear whether the Lys is attached to the C-terminal amino acid of the GLP-1 or Asp-Lys.

Applicants respectfully traverse these rejections and address each in turn.

1) how different the derivative of GLP-1 or GLP-2 is to the parent compound (ie GLP-1

or GLP-2 and analogs or fragments thereof) is explicitly stated in each of the claims; namely that the derivative differs from the parent compound by having a lipophilic substituent attached to the N-or C-terminus of the parent peptide optionally via a spacer. Accordingly, Applicants submit that the phrase a derivative of GLP-1 or GLP-2 is clear and definite and fully complies with the requirements of 35 USC 112, second paragraph.

2) The lack of antecedent basis is rendered moot by the amendment to claims 20 and 34 to recite that the "lipophilic substituent is a straight chain fatty acid optionally having an amino group..."

3) The Lys in Glu-Lys or Asp-Lys is attached to both the Glu or the Asp and to the C-terminal amino acid of the peptide.

Accordingly, in view of the above amendments and remarks, Applicants respectfully request withdrawal of the section 112, second paragraph rejections.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Please charge any deficiencies or overpayment to Deposit Account No. 14-1447.

Respectfully submitted,

Date: November 27, 2002

Richard W. Bork

Richard W. Bork, Reg. No. 36,459
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

"Marked-Up" Version of Amendments to the Specification

Please replace the paragraph at page 9, line 26 to page 10, line 5 with the following:

--For-Nle-Leu-Phe-Nle-Tyr-Lys-OH (SEQ ID NO: [6] 7), was purchased from Bachem Feinchemikalien AG, Switzerland. The peptide is a potent chemoattractant for human neutrophils. The title compound was prepared by dissolving 17 mg of For-Nle-Leu-Phe-Nle-Tyr-Lys-OH (SEQ ID NO: [6] 7) in 5 ml of DMF and then adding 35 µl l of triethylamine followed by 20 mg of solid tetradecanoic acid succinimidyl-N-hydroxy ester to the solution. The reaction was monitored by RP-HPLC employing a column packed with reversed phase C18 silica material. For the elution was used a gradient from 30% ethanol to 80 % ethanol in 0.1% aqueous TFA. The product was purified on a column (length 250 mm diameter 20 mm) packed with C18 silica reversed phase material. The compound was dissolved in 74% ethanol/0.1% aqueous TFA and subsequently applied to the column and purified at 40 °C by isocratic elution in the same buffer at a flow rate of 6 ml/hour. The yield was 20 mg. The identity of the compound was confirmed by PDMS.--

Please replace the paragraph at page 10, lines 12-16 with the following:

--Reference

The reference compound, For-Nle-Leu-Phe-Nle-Tyr-Lys-OH (SEQ ID NO: [6] 7), was purchased from Bachem Feinchemikalien AG, Switzerland, and used as received. The lipophilicity of the reference compound relative to human insulin was found to be 2.3.--

Please replace the paragraph at page 10, lines 19-20 with the following:

--EXAMPLE 2

Synthesis of H-Tyr-D-Ala-Gly-Phe-Leu-Lys(N^{ε}-tetradecanoyl)-OH (SEQ ID NO: [7] 8).--

Please replace the paragraph at page 10, lines 23-31 with the following:

--The enkephalin derivative H-Tyr-D-Ala-Gly-Phe-Leu-Lys(N^{ε}-tetradecanoyl)-OH (SEQ ID NO: [7] 8) was made from Boc-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: [7] 9) (A-2435 Bachem Feinchemikalien AG, Switzerland). The Boc-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: [7] 9) was acylated using tetradecanoic acid succinimidyl-N-hydroxy ester as described in Example 1. The reaction mixture was evaporated to dryness and the residue was dissolved in TFA and evaporated to dryness, solubilized in ethanol/water/0.1% and purified by RP-HPLC as described in Example 1. The yield was 15 mg.--

Please replace the paragraph at page 11, lines 1-7 with the following:

--Reference

The reference compound, H-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: [7] 10), was synthesized from Boc-Tyr-D-Ala-Gly-Phe-Leu-Lys-OH (SEQ ID NO: [7] 9)by dissolving 20 mg of this compound in 200 µl of TFA and evaporating to dryness. The residue was dissolved in 5% acetic acid and freeze dried. The lipophilicity of the reference compound relative to human insulin was found to be $3.0x10^{-3}$.--

Please replace the paragraph at page 11, lines 10-12 with the following:

--EXAMPLE 3

Synthesis of H-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys(N^{ε}-tetradecanoyl)-OH (SEQ ID NO: [8] 11).--

Please replace the paragraph at page 11, lines 15-22 with the following:

--Fmoc-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: [8] 12) (obtained from Bachem Feinchemikalien AG, Switzerland) which is a potent inhibitor of renin was allowed to react with tetradecanoic acid succinimidyl-N-hydroxy ester as described in Example 1. After the acylation reaction, the Fmoc group was removed by addition of piperidine to the reaction mixture to a final concentration of 20%. The title compound was isolated by RP-HPLC as described in Example 1. The yield was 23 mg.--

Please replace the paragraph at page 11, lines 29-36 with the following:

--Reference

The reference compound, H-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: [8]

13), was synthesized from Fmoc-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: [8] 12) (obtained from Bachem Feinchemikalien AG, Switzerland). Thus, 20 mg of Fmoc-Pro-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys-OH (SEQ ID NO: [8] 12) was dissolved in 500 µl of 20% piperidine in DMF and left for 20 min. The reference compound was purified by RP-HPLC as described in Example 1.--

Please replace the paragraph at page 14, lines 6-15 with the following:

--Human (H-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-Lys(N^{ϵ}-tetradecanoyl)-COOH) (SEQ ID NO: [9] 14) was synthesized by standard Fmoc solid phase peptide synthesis (Methods in Molecular Biology, Vol 35: Peptide Synthesis Protocols). The ε-amino group of the C-terminal lysine was acylated using tetradecanoic acid succinimidyl-N-hydroxy ester according to the procedure described below. The synthesis was performed manually in polypropylene syringes, on a resin based on a low cross linked polystyrene backbone grafted with polyoxyethylene (TentaGel Resin).--

"Marked-Up" Version Of Amendments To The Claims

20. (Amended) A derivative of GLP-1 or an analog or fragment thereof wherein a lipophilic substituent optionally via a spacer is attached to the N-terminal amino acid of GLP-1 or the analog or fragment thereof and wherein the lipophilic substituent is a straight chain fatty acid optionally having an amino group and having 8 to 40 carbon atoms and the spacer is succinic acid, Glu or Asp.

34. (Amended) A derivative of GLP-2 or an analog or fragment thereof wherein a lipophilic substituent optionally via a spacer is attached to the N-terminal amino acid of GLP-2 or the analog or fragment thereof and wherein the lipophilic substituent is a straight chain fatty acid optionally having an amino group and having 8 to 40 carbon atoms and the spacer is succinic acid, Glu or Asp.